

FORMATION OF HETEROCYCLES

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Abstract

Complex heterocyclic compounds are synthesized from anilide-linked-alkenes in a single step by a cascade reaction using O-iodoxybenzoic acid (IBX) as a mediator. Alternative, the same complex heterocyclic compounds may be synthesized in a two step process using O-iodoxybenzoic acid (IBX) as a mediator and starting from common and commercially available substrate materials.

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Description

FORMATION OF HETEROCYCLES

Specification

Technical Field:

The present invention relates to the cyclization of anilide-linked-alkenes and related compounds to form anilide-linked-heterocycles. More particularly, the present invention relates to a cascade reaction wherein anilide-linked-alkene and related compounds undergo a cyclization mediated by O-iodoxybenzoic acid (IBX) to form the anilide-linked-heterocycle.

Background:

What is needed is a one step synthetic protocol for the production of anilide-linked heterocycles from anilide-linked-alkenes and related substrates employing O-iodoxybenzoic acid (IBX) as an oxidant. What is also needed is a two step synthetic protocol for the production of anilide-linked-heterocycles from ubiquitous and commercially available starting materials.

Summary:

It is disclosed herein that N-phenyl γ -lactams and a variety of other heterocycles including oxazolidinones, thioxazolidinones, and cyclic ureas and thioureas can be produced in high yields by reacting γ -alkeno amides with o-iodoxybenzoic acid (IBX). IBX, i. e., 1-hydroxy-1,2-benziodoxol-3(1H)-one 1-oxide, is a precursor to Dess-Martin periodinane (DMP) and is prepared according to the method of M. Frigerio, et al, J. Org. Chem. 1999, 64, 4537-4538. IBX is known to be a selective oxidant for alcohols (M. Frigerio, et al, Tetrahedron Lett. E. J. Corey, et al., Tetrahedron Lett. 1995, 36, 3485-3488). This simple reaction represents a fundamentally new strategy for the construction of molecular diversity relevant to biological screening and drug discovery (see Scheme 1).

More particularly, a plethora of simple as well as complex γ -alkeno amides have been shown to participate in an IBX-mediated cyclization reaction leading to a variety of novel structures (Table 1). Significantly, the reaction is unbiased to substitution on the aryl moiety, with the one exception of the nitro group, in which case the reaction does not proceed under the normal conditions. Substrates which harbor electron-donating groups (e. g. Table 1, entry 6), electron-withdrawing groups (e. g. Table 1, entries 4 and 7), halides (e. g. Table 1, entries 2, 15 and 17), and sterically encumbered groups (e. g. Table 1, entry 8) situated at the ortho, meta positions all proceed smoothly and in high yields.

One aspect of the invention is directed to a one-step process for converting an anilidelinked-alkene to a anilide-linked-heterocycle. The anilide is characterized as having a benzene ring, an anilide nitrogen attached to the benzene ring, and an oxo or thioxo group attached to the anilide nitrogen. The anilide is linked to the alkene at the oxo or thioxo group.

The alkene includes a carbon, oxygen or nitrogen linkage with the oxo or thioxo group. The alkene has a γ , δ unsaturation with respect to the oxo or thioxo group. The anilide and alkene each optionally have one or more substituents. During the one step process, the anilidelinked-alkene is cyclized by treatment with o-iodoxybenzoic acid (IBX) for producing the anilide-linked-heterocycle. The anilide-linked-heterocycle includes the benzene ring of the anilide and a heterocycle. The heterocycle is a five membered ring incorporating the anilide nitrogen and the oxo or thioxo group. The heterocycle is linked to the benzene ring of the anilide by the anilide nitrogen.

In another aspect of the invention, the above process is enlarged including an additional step directed to the synthesis of the anilide-linked-alkene substrate from simple starting materials. In a preferred mode, the synthesis of the substrate is achieved in one step.

Accordingly, the overall synthesis of complex anilide-linked-heterocycles from simple starting materials can be achieved by this method in as little as two steps. Accordingly, prior to the above cyclization step, an aryl amine is coupled by condensation with a γ , δ -unsaturated carboxylic acid or a thiocarboxylic acid for producing the anilide-linked-alkene.

An exemplary condensation reaction is represented as follows:

In the above reaction, the oxo groups represented in the above structures may be optionally replaced by thioxo groups. When the above anilide-linked-alkene is then cyclized, the anilide-linked-heterocycle looks like the following:

Once again, the oxo group represented in the above structure be optionally replaced by a thioxo group. In the above structures, X1 is oxygen or sulfur; and X2 (not shown) is carbon.

However, the preferred substituents for R'a, R'b, and R''', i. e., the substituents on the anilide benzene ring, are unchanged as compared to the earlier example. Additionally, the preferred substituents for the alkene, i. e., R3, R4, R5, and R6, are also substantially identical to the earlier example. However, because X2 is carbon in this example, variable substituents may be employed at that position, i. e., R2. Preferred substituents for R are substantially identical to the preferred substituents for R3, R4, R5, and R6.

In addition to the above condensation reaction, other protocols may also be employed for synthesizing the anilide-linked-alkene substrate from simple starting materials, each employing only one step. In each instance, the substituents on the anilide benzene ring and the alkene are limited by the available starting materials, the chemistry of the synthesis of the substrate, and the chemistry of the subsequent cyclization reaction. Preferred methodologies for synthesizing the anilide-linked-alkene include the following:

Coupling an isocyanate or thioisocyanate with a P, γ -unsaturated alcohol or thiol for producing the anilide-linked-alkene, as represented by the following reaction:

Coupling an isocyanate or thioisocyanate with a P, γ -unsaturated amine for producing the anilide-linked-alkene selected from a group consisting of 1-aryl-3-alkenylurea and 1-aryl-3-alkenylthiourea, as represented by the following reaction:

Coupling a P, γ -unsaturated alcohol or thiol with an aryl amine and phosgene or thiophosgene in a three way reaction for producing the anilide-linked-alkene selected from a group consisting of arylcarbamoyl-alkene and arylthiocarbamoyl-alkene, as represented by the following reaction:

Coupling a 3, γ -unsaturated amine with an aryl amine and phosgene or thiophosgene in a three way coupling for producing the anilide-linked-alkene, as represented by the following reaction:

Brief Description of Drawings:

Figure 1 illustrates a process for the synthesis of novel heterocycles. Anilide-linked heterocycles are produced from anilide-linked-alkenes using IBX as a mediator. More particularly, the reaction of unsaturated aryl amides, carbamates, thiocarbamates and ureas with IBX is illustrated.

Figure 2 illustrates a tentative mechanism for the IBX-mediated cyclization of arylamido alkenes.

Figure 3 illustrates a tentative mechanism of the conversion of cyclopropane 37 to cyclobutene 38.

Figure 4 illustrates a tentative mechanism for the radical cascade conversion of 39 to 40.

Figure 5 illustrates that a precise electronic environment is required in order to activate an amide for reaction with IBX.

Figure 6 is a table illustrating the IBX-mediated cyclization of amido alkenes to form heterocycles.

Figure 7 is a table illustrating the IBX-mediated cyclization of carbamates to form oxazolidinones and their hydrolysis to 1,2 cis-N-phenyl amino alcohols.

Figure 8 is a table illustrating the IBX-mediated cyclization of thionocarbamates and open-chain ureas and thioureas to form thionooxazolidinones, cyclic ureas, and thioureas.

Figure 9 illustrates three preferred methodologies for producing exemplary anilidelinked-alkenes employable as substrates. Exemplary commercially available starting materials for each of the three methodologies are illustrated in Figures 10-14. In methodology 1, anilines are mixed with γ -alkeno carboxylic acids in the presence of EDC (1-(-3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride) to produce an anilide-linked alkene wherein the alkene includes a carbon which is attached to the oxo group of the anilide.

In methodology 2, arylisocyanates or aryliso (thio) cyanates are mixed with allylic alcohols or allylic amines to produce an anilide-linked-alkene wherein the alkene includes an oxygen or nitrogen which is attached to the oxo or thio group of the anilide. In methodology 3, anilines are mixed with allylic alcohols or allylic amines in the presence of phosgene or thiophosgene to produce an anilide-linked-alkene wherein the alkene includes a nitrogen which is attached to the oxo or thio group of the anilide.

Figure 10 illustrates 50 exemplary anilines employable in methodologies 1 and 3 of

Figure 9. Over 4000 other anilines were commercially available in 1999.

Figure 11 illustrates 20 exemplary arylisocyanates employable in methodology 2 of

Figure 9. Over 175 arylisocyanates and over 25 arylisothiocyanates (not shown) were commercially available in 1999.

Figure 12 illustrates 25 exemplary γ -alkeno carboxylic acids employable in methodology 1 of Figure 9. Over 200 other γ -alkeno carboxylic acids and 150 γ -alkeno carboxylic esters were commercially available in 1999.

Figure 13 illustrates 30 exemplary allylic alcohols employable in methodologies 2 and 3 of Figure 9. Over 300 other allylic alcohols and several hundred allylic esters were commercially available in 1999.

Figure 14 illustrates 10 exemplary allylic amines employable in methodologies 2 and 3 of Figure 9. Over 50 other allylic amines were commercially available in 1999. Allylic amines could also be easily obtained from several hundred allylic alcohols, e. g., according to the following steps: 1. MsCl ; 2. NaN_3 ; 3. $\text{Ph}_3\text{H}_2\text{O}$.

Figure 15 illustrates an IBX mediated reaction with a bis anilide-linked-alkene.

Detailed Description:

The preferred methodologies for constructing the anilide-linked-alkene substrates are illustrated in Figure 9. There is a plethora of readily available building blocks that correspond to the starting materials for this substrate. The generality of this two-step sequence for the construction of molecular diversity is demonstrated in Figures 6-8.

Remarkably, oxazolidinones (19b-26b, Figure 7); thioxazolidinones (product of entry 3, Figure 8) and cyclic ureas and thioureas (products of entries 9 and 10, Figure 7) are readily available from the corresponding carbamates, thionocarbamates and open-chain ureas and thioureas, respectively, using this straightforward protocol. Hydrolysis of the oxazolidinones (NaOH/EtOH) permits access to cis-N-phenyl 1,2-amino alcohols (27-32, Figure 7). The challenging task of establishing quaternary centers (e. g. Figure 6, entries 16-17; Figure 7, entry 5) including spiro compounds such as 25b proceeds smoothly without loss of efficiency.

The procedure is operationally extremely simple and involves dissolution of the substrate and IBX in $\text{THF}:\text{DMSO}$ (10: 1) in a sealed tube and heating at 90 C for a number of hours. The reaction is impervious to air or water, producing the desired products even using water as a co-solvent. The high efficiency and reliability of this IBX-mediated reaction was not diminished even in the case of bis-amide, wherein cyclization occurred, in 84%, to furnish the polycycle (Figure 15).

The IBX-mediated cyclization appears to proceed through an amide-centered reactive intermediate, such as a radical, as indicated in Figure 2. The precise steps leading to these intermediates cannot be confidently defined at present, nor can the exact nature of this intermediate. IBX may interact with anilides to produce a species which behaves as an amidyl radical (A.-C. Callier, et al., *Tetrahedron Lett.* A.-C. Callier, et al., *Tetrahedron Lett.* M. Newcomb, et al., *Tetrahedron Lett.* 1991,32, 1035-1038; M. Newcomb, et al., *Tetrahedron Lett.* A. J. Clark, et al., *Tetrahedron Lett.* 1999,441-443; and A. J.

Clark, et al., *Synlett* 1999,444-446). It is proposed herein that the species which behaves as an amidyl radical is then engages the proximate olefin in a 5-exo-trig fashion followed by a hydrogen abstraction,

presumably from the solvent. Mechanistic studies of the reaction of alcohols with IBX have been performed, e. g., S. De Munari, et al., J. Org. Chem. 1996, 61, 9272-9279; and M. Frigerio, et al., I. Org. Chem. In contrast to the mechanistic studies of the reaction of alcohols with IBX, NMR studies on the present reaction indicate that anilides do not form stable intermediates with this reagent. A 0.05 mmol scale reaction was performed in DMSO-d₆ at varying temperatures (25-110 °C) in an NMR tube. No intermediates could be detected; only product formation and some decomposition of IBX was observed. The complexes of anilides with IBX might, therefore, be short-lived. Additional evidence for the radicaloid character of the reaction is seen in Table 1, entry 9 in which case a 1:1 ratio of diastereoisomers was obtained indicating a disordered transition state as expected from such a pathway.

The present process is demonstrated to proceed only with anilides, suggesting the requirement for a proper electronic environment surrounding the nitrogen. Although the reason for this requirement remains unknown, the aryl moiety of these systems may assume an active role in the reaction, i. e., the aryl moiety is more than just stabilizing.

The structural types produced by the reactions disclosed herein are found in innumerable natural products and medicinally important compounds and as such these processes may find important applications in organic synthesis. A literature search using SciFinder (ACS) to probe the popularity of these structural types in natural products and medicinally important compounds led to over 50,000 hits. The potential that these functionalities have for further elaboration to other scaffolds is nearly infinite. The following are some selected examples: Natural products: Yunnaneic acids A-D (uremic toxin-decreasing effects): T. Takashi, et al., J. Nat. Prod.; Isoschizogamine (HIV inhibitor): J. Hajicek, et al., Tetrahedron Lett. G.

T. Tan, et al., J. Nat. Prod. Medicinally important compounds: a) (therapeutic CNS agents) M. Varasi, et al., (Pharmacia S. p. A., Italy), International application WO 95-EP1650; b) (5-HT₃ antagonists) M. Varasi, et al., (Farmitalis Carlo Erba S. R. L., Italy), International application WO 93-EP1498; c) (antihyperlipidemics) S. Yano, et al., (Taiho Pharmaceutical Co., Ltd., Japan), Patent Application WO 93JP559; d) (hypolipemics and hypoglycemics) H. Yanagisawa, et al., (Sankyo Co., Japan) Patent Application JP 95-162442; e) (monoamine oxidase inhibitors) C. Banzati, et al., I.

Heterocycl. Chem. 1983, 20, 139-140; f) (antidepressant) (Erba, Carlo S. p. A., Italy) Patent Application IT 75-30829.

Furthermore, the extraordinary ease with which the starting materials for these reactions can be prepared, coupled with the striking complexity which is attainable in one step makes this protocol ideal for the generation of manifold libraries of relevant compounds for biological screening and chemical biology purposes.

Experimental Section:

To a solution of 16a (0.1 mmol) in THF: DMSO (10:1, 4 mL total volume) was added 2.0 equiv of IBX. To complete the reaction, the solution was placed in a sealed tube and heated for 12 h at 90 °C, followed by addition of another 2.0 equiv of IBX and heating for a further 12 h period at the same temperature. The reaction mixture was diluted with EtOAc and washed with 5% aq. NaHCO₃ and brine, dried over MgSO₄, and concentrated. After purification by preparative thin layer (PTLC) chromatography (silica gel, EtOAc: hexane 1:2), compound 16b was obtained in 88% yield (see Table 3 for selected physical properties).

Data for selected compounds:

16b: Colorless cubic crystals; m. p. 238-239 °C, (acetone-hexane); R_f = 0.37 [silica gel, EtOAc: hexane 1:2]; IR (film) K = 2968, 2865.

24b: R_f 0.25 [silica gel, ethyl acetate: hexane 1:1]; [C]_D = -175 (c 0.04, CHCl₃); IR (film) C_{max} = 2920, 2848, 1736, 1598, 1499, 1401, 1242, 1206, 1164, 1122, 1087, 1011 cm⁻¹.

30: R_f = 0.4 [silica gel, ethyl acetate: methylene chloride 1:1]; [α]_D = -250 (c 0.1, CHCl₃); IR (film) (xma.) = 3380, 2361, 1602, 1503, 1432, 1321, 1262, 1099, 751 cm⁻¹.

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Claims

What is claimed is: 1. A process for converting an anilide-linked-alkene to a anilide-linked-heterocycle, the anilide having a benzene ring, an anilide nitrogen attached to the benzene ring, and an oxo or thioxo group attached to the anilide nitrogen, the anilide being linked to the alkene at the oxo or thioxo group, the alkene including a carbon, oxygen or nitrogen linkage with the oxo or thioxo group, the alkene having a y, 6 unsaturation with respect to the oxo or thioxo group, the anilide and alkene each optionally having one or more substituents, the process comprising the following step:

cyclizing the anilide-linked-alkene by treatment with o-iodoxybenzoic acid (IBX) for producing the anilide-linked-heterocycle, the anilide-linked-heterocycle including the benzene ring of the anilide and a heterocycle, the heterocycle being a five membered ring incorporating the anilide nitrogen and the oxo or thioxo group, the heterocycle being linking to the benzene ring of the anilide by the anilide nitrogen.

2. The process according to claim 1 wherein the anilide-linked-alkene is represented by the following structure:

the anilide-linked-heterocycle is represented by the following structure:

wherein: X1 is selected from the group consisting of oxygen and sulfur; X2 is selected from the group consisting of carbon, oxygen, and nitrogen; R1a, R'b, and R1c are each independently selected from a group of terminal and non-terminal

radicals, the non-terminal radicals potentially including further extensions with one or more of the terminal or non-terminal radicals,

the terminal radicals being selected from the group consisting of hydrogen; alkyl; aryl; alkenyl; allyl; trialkylsilyl; alkylidiarylsilyl; dialkylarylsilyl;

tri (alkoxy) silyl; fluorine; chlorine; bromine; cyanide; alkoxy; orthoformyl; trialkylsiloxy; acyloxy that include an aryloxy, alkoxy, aryl, alkyl or alkenyl radical; aryloxy; trifluoromethyl; sulphonyl; and acyl that include an alkyl, alkenyl, or aryl radical; and

the non-terminal radicals are selected from the group consisting of alkyl; cyclic alkyl; fully or partially saturated ring alkyl fused to the benzene ring of the anilide at R'a and R'b or at R1b and R'c; partially saturated alkene; partially saturated alkene ring; aryl; heteroaromatic that excludes sulfur; heterocyclic that excludes sulfur except as sulphone; heterocyclic that are partially or fully saturated fused to the benzene ring of the anilide at R'a and R1b or R1b and R1c that exclude sulfur except as the sulphone moiety; ketone; ester; ketal; acetal; ether; dialkylarylamine; nitrile; amide except amide having a nitrogen bonded to hydrogen and an aryl group; urea except urea having a nitrogen bonded to hydrogen and an aryl group; thioamide except thioamide having a nitrogen bonded to hydrogen and an aryl group; thiourea except thiourea having a nitrogen bonded to hydrogen and an aryl group; urethane except urethane having a nitrogen bonded to hydrogen and an aryl group; thiourethane except thiourethane having a nitrogen bonded to hydrogen and an aryl group;

(X, 3-unsaturated ketone or ester; sulphone; sulphonamide; imide; diarylketone; lactone; lactam; lactim; sultam; sultim; allylsilane; arylsilane; vinylsilane; alkylsilane; silyl ether; siloxane; orthosilicate; silicate; carbonate; orthoester;

with the proviso that at least one ortho position of the anilide must be hydrogen and not occupied by R'a, R'b, or R"; and R3, R4, and Rs are each independently selected from a group of terminal and non

terminal radicals, the non-terminal radicals potentially including further extensions with one or more terminal or non-terminal radicals,

the terminal radicals being selected from the group consisting of hydrogen; alkyl; aryl; alkenyl; allyl; alkynyl; propargyl; trialkylsilyl; alkylidiarylsilyl;

dialkylarylsilyl; tri (alkoxy) silyl; fluorine; chlorine; bromine; cyanide; alkoxy; orthoformyl; trialkylsiloxy; acyloxy that include an aryl, alkyl or alkenyl radical; aryloxy; trifluoromethyl; sulphonyl; and acyl that include an alkyl, alkenyl, or aryl radical; and

the non-terminal radicals being selected from a group consisting of alkyl; cyclic alkyl; bridging saturated or partially saturated alkyl ring; bridging heterocyclic

ring not containing sulfur except as the sulphone moiety; olefin; cyclic olefin; aryl; alkynyl; heteroaromatic not containing sulfur; heterocyclic group not containing sulfur except as a sulphone; ketone; ester; ketal; acetal; ether; dialkylarylamine; nitrile; amide except amide having a nitrogen bonded to hydrogen and an aryl group; urea except urea having a nitrogen bonded to hydrogen and an aryl group; thioamide except thioamides having a nitrogen bonded to hydrogen and an aryl group; thiourea except thiourea having a nitrogen bonded to hydrogen and an aryl group; urethane except urethane having a nitrogen bonded to hydrogen and an aryl group; thiourethane except thiourethanes having a nitrogen bonded to hydrogen and an aryl group; oc, P-unsaturated ketone or ester; sulphone; sulphonamide; imide; diarylketone; lactone; lactam; lactim; sultam; allylsilane; arylsilane; vinylsilane; alkylsilane; silyl ether; siloxane; orthosilicate; silicate; carbonate; orthoester; with the proviso that R₂, R₃, R₄, R₅ cannot be fluorine, chlorine, bromine, cyanide, amino, alkylamino, dialkylamino, arylamino, diarylamino, arylamido, arylthioamido, arylcarbamoyl, arylthiocarbamoyl, alkoxy, trialkylsilyloxy, or acyloxy radicals that incorporate alkyl, alkenyl, or aryl radicals; with the further proviso that R₂, R₃, R₄, R₅ cannot include any radical that has a double or triple bond or an aryl or heteroaromatic groups that is conjugated with the, 6 unsaturation of the anilide-linked-alkene; with the further proviso that R₅ cannot be a sulphonyl radical, a vinylic radical unless a complex mixture of products is desired or R₅ is the same as CR radical.

3. The process, according to claim 1, further comprising the following additional step, performed prior to said polycyclizing step:

coupling an aryl amine with a, 6-unsaturated carboxylic acid or a thiocarboxylic acid for producing the anilide-linked-alkene, as represented by the following exemplary reaction:

the oxo groups represented in the above structures being optionally replaced by thioxo groups; and the anilide-linked-heterocycle from said polycyclizing step is represented by the following structure:

the oxo group represented in the above structure being optionally replaced by a thioxo group; wherein the anilide-linked-alkene resulting from said coupling step and the anilide-linked heterocycle resulting from said polycyclizing step are limited as follows:

X₁ is selected from the group consisting of oxygen and sulfur;

X₂ is carbon;

R'_a, R'_b, and R'_c are each independently selected from a group of terminal and non-terminal radicals, the non-terminal radicals potentially including further extensions with one or more of the terminal or non-terminal radicals,

the terminal radicals being selected from the group consisting of hydrogen; alkyl; aryl; alkenyl; allyl; trialkylsilyl; alkylidiarylsilyl; dialkylarylsilyl;

tri (alkoxy) silyl; fluorine; chlorine; bromine; cyanide; alkoxy; orthoformyl; trialkylsiloxy; acyloxy that include an aryloxy, alkoxy, aryl, alkyl or alkenyl radical; aryloxy; trifluoromethyl; sulphonyl; and acyl that include an alkyl, alkenyl, or aryl radical; and

the non-terminal radicals are selected from the group consisting of alkyl; cyclic alkyl; fully or partially saturated ring alkyl fused to the benzene ring of the anilide at R'_a and R'_b or at R'_b and R'_c; partially saturated alkene; partially saturated alkene ring; aryl; heteroaromatic that excludes sulfur; heterocyclic that excludes sulfur except as sulphone; heterocyclic that are partially or fully saturated fused to the benzene ring of the anilide at R'_a and R'_b or R'_b and R'_c that exclude sulfur except as the sulphone moiety; ketone; ester; ketal; acetal; ether; dialkylarylamine; nitrile; amide except amide having a nitrogen bonded to hydrogen and an aryl group; urea except urea having a nitrogen bonded to hydrogen and an aryl group; thioamide except thioamide having a nitrogen bonded to hydrogen and an aryl group; thiourea except thiourea having a nitrogen bonded to hydrogen and an aryl group; urethane except urethane having a nitrogen bonded to hydrogen and an aryl group; thiourethane except

thiourethane having a nitrogen bonded to hydrogen and an aryl group;
 (X, p-unsaturated ketone or ester; sulphone; sulphonamide; imide; diarylketone;
 lactone; lactam; lactim; sultam; sultim; allylsilane; arylsilane; vinylsilane;
 alkylsilane; silyl ether; siloxane; orthosilicate; silicate; carbonate; orthoester;
 with the proviso that at least one ortho position of the anilide must be hydrogen and
 not occupied by R'a, R", or Rlc; and R2, R3, R4, R5, and R6 are each independently selected from a group
 of terminal and non
 terminal radicals, the non-terminal radicals potentially including further extensions
 with one or more terminal or non-terminal radicals,
 the terminal radicals being selected from the group consisting of hydrogen; alkyl;
 aryl; alkenyl; allyl; alkynyl; propargyl; trialkylsilyl; alkylarylalkyl;
 dialkylarylsilyl; tri (alkoxy) silyl; fluorine; chlorine; bromine; cyanide; alkoxy;
 orthoformyl; trialkylsiloxy; acyloxy that include an aryl, alkyl or alkenyl
 radical; aryloxy; trifluoromethyl; sulphonyl; and acyl that include an alkyl,
 alkenyl, or aryl radical; and
 the non-terminal radicals being selected from a group consisting of alkyl; cyclic
 alkyl; bridging saturated or partially saturated alkyl ring; bridging heterocyclic
 ring not containing sulfur except as the sulphone moiety; olefin; cyclic olefin;
 aryl; alkynyl; heteroaromatic not containing sulfur; heterocyclic group not
 containing sulfur except as a sulphone; ketone; ester; ketal; acetal; ether;
 dialkylarylamino; nitrile; amide except amide having a nitrogen bonded to
 hydrogen and an aryl group; urea except urea having a nitrogen bonded to
 hydrogen and an aryl group; thioamide except thioamides having a nitrogen
 bonded to hydrogen and an aryl group; thiourea except thiourea having a
 nitrogen bonded to hydrogen and an aryl group; urethane except urethane
 having a nitrogen bonded to hydrogen and an aryl group; thiourethane except
 thiourethanes having a nitrogen bonded to hydrogen and an aryl group;
 (X, P-unsaturated ketone or ester; sulphone; sulphonamide; imide; diarylketone;
 lactone; lactam; lactim; sultam; sultim; allylsilane; arylsilane; vinylsilane;
 alkylsilane; silyl ether; siloxane; orthosilicate; silicate; carbonate; orthoester;
 with the proviso that R4, R5, R6 cannot be fluorine; chlorine; bromine; cyanide;
 amino; alkylamino; dialkylamino; arylamino; diarylamino; arylamido;
 arylthioamido; arylcarbonyl; arylthiocarbonyl; alkoxy; trialkylsiloxy; and
 acyloxy wherein the acyloxy radical incorporates an alkyl, alkenyl, or aryl
 radical;
 with the further proviso that R4, R5, R6 cannot be a radical that includes a double or
 triple bond or an aryl or heteroaromatic group that is conjugated with the y, 8
 unsaturation of the anilide-linked-alkene.

4. The process, according to claim 1, further comprising the following additional step, performed prior to
 said polycyclizing step:

coupling an isocyanate or thioisocyanate with a P, γ -unsaturated alcohol or thiol for producing the
 anilide-linked-alkene, as represented by the following reaction:

and the anilide-linked-heterocycle from said polycyclizing step is represented by the following structure:

wherein the anilide-linked-alkene resulting from said coupling step and the anilide-linked heterocycle
 resulting from said polycyclization step are limited by said coupling step as follows:

XI is selected from the group consisting of oxygen and sulfur;

* is oxygen or sulfur;

R1a, R1b, and R' are each independently selected from a group of terminal and non-terminal
 radicals, the non-terminal radicals potentially including further extensions with one or
 more terminal or non-terminal radicals,

the terminal radicals being selected from the group consisting of hydrogen; alkyl;
 aryl; alkenyl; allyl; trialkylsilyl; alkylarylalkyl; dialkylarylsilyl;

tri (alkoxy) silyl; fluorine; chlorine; bromine; cyanide; alkoxy; orthoformyl;
 trialkylsiloxy; acyloxy that include an aryloxy, alkoxy, aryl, alkyl or alkenyl
 radical; aryloxy; trifluoromethyl; sulphonyl; and acyl that include an alkyl,
 alkenyl, or aryl radical; and

the non-terminal radicals are selected from the group consisting of alkyl; cyclic
 alkyl; fully or partially saturated ring alkyl fused to the benzene ring of the
 anilide at R1a and R1b or at R' and Rlc; partially saturated alkene; partially

saturated alkene ring; aryl; heteroaromatic that excludes sulfur; heterocyclic that excludes sulfur except as sulphone; heterocyclic that are partially or fully saturated fused to the benzene ring of the anilide at R1a and R'b or R'b and R1c that exclude sulfur except as the sulphone moiety; ketone; ester; ketal; acetal; ether; dialkylarylamine; nitrile; amide except amide having a nitrogen bonded to hydrogen and an aryl group; urea except urea having a nitrogen bonded to hydrogen and an aryl group; thioamide except thioamide having a nitrogen bonded to hydrogen and an aryl group; thiourea except thiourea having a nitrogen bonded to hydrogen and an aryl group; urethane except urethane having a nitrogen bonded to hydrogen and an aryl group; thiourethane except thiourethane having a nitrogen bonded to hydrogen and an aryl group; a -unsaturated ketone or ester; sulphone; sulphonamide; imide; diarylketone; lactone; lactam; lactim; sultam; sultim; allylsilane; arylsilane; vinylsilane; alkylsilane; silyl ether; siloxane; orthosilicate; silicate; carbonate; orthoester; with the proviso that at least one ortho position of the anilide must be hydrogen and not occupied by R'a, R''', or R''; and R2, R3, R4, and R5 are each independently selected from a group of terminal and non terminal radicals, the non-terminal radicals potentially including further extensions with one or more terminal or non-terminal radicals, the terminal radicals being selected from the group consisting of hydrogen; alkyl; aryl; alkenyl; allyl; alkynyl; propargyl; trialkylsilyl; alkyl-diarylsilyl; dialkylarylsilyl; tri (alkoxy) silyl; fluorine; chlorine; bromine; cyanide; alkoxy; orthoformyl; trialkylsiloxy; acyloxy that include an aryl, alkyl or alkenyl radical; aryloxy; trifluoromethyl; sulphonyl; and acyl that include an alkyl, alkenyl, or aryl radical; and the non-terminal radicals being selected from a group consisting of alkyl; cyclic alkyl; bridging saturated or partially saturated alkyl ring; bridging heterocyclic ring not containing sulfur except as the sulphone moiety; olefin; cyclic olefin; aryl; alkynyl; heteroaromatic not containing sulfur; heterocyclic group not containing sulfur except as a sulphone; ketone; ester; ketal; acetal; ether; dialkylarylamine; nitrile; amide except amide having a nitrogen bonded to hydrogen and an aryl group; urea except urea having a nitrogen bonded to hydrogen and an aryl group; thioamide except thioamides having a nitrogen bonded to hydrogen and an aryl group; thiourea except thiourea having a nitrogen bonded to hydrogen and an aryl group; urethane except urethane having a nitrogen bonded to hydrogen and an aryl group; thiourethane except thiourethanes having a nitrogen bonded to hydrogen and an aryl group; a, -unsaturated ketone or ester; sulphone; sulphonamide; imide; diarylketone; lactone; lactam; lactim; sultam; sultim; allylsilane; arylsilane; vinylsilane; alkylsilane; silyl ether; siloxane; orthosilicate; silicate; carbonate; orthoester; with the proviso that R', R3, R4, R5 cannot be fluorine, chlorine, bromine, cyanide, amino, alkylamino, dialkylamino, arylamino, diarylamino, arylamido, arylthioamido, arylcarbonyl, arylthiocarbonyl, alkoxy, trialkylsiloxy, or acyloxy radicals that incorporate alkyl, alkenyl, or aryl radicals; with the further proviso that R2, R3, R4, R5 cannot include any radical that has a double or triple bond or an aryl or heteroaromatic groups that is conjugated with the γ , δ unsaturation of the anilide-linked-alkene; with the further proviso that R5 cannot be a sulphonyl radical, a vinylic radical unless a complex mixture of products is desired or R5 is the same as CR4CR2R3 radical.

5. The process, according to claim 1, further comprising the following additional step, performed prior to said polycyclizing step:

coupling an isocyanate or thioisocyanate with a P, γ -unsaturated amine for producing the anilide-linked-alkene selected from a group consisting of 1-aryl-3-alkenylurea and 1-aryl-3-alkenylthiourea, as represented by the following reaction:

and the anilide-linked-heterocycle from said polycyclizing step is represented by the following structure:

wherein the anilide-linked-alkene resulting from said coupling step and the anilide-linked heterocycle resulting from said polycyclization step are limited by said coupling step as follows:

X1 is selected from the group consisting of oxygen and sulfur;

X2 is nitrogen;

R1a, R1b, and R1c are each independently selected from a group of terminal and non-terminal radicals; the non-terminal radicals potentially including further extensions with one or more of the terminal or non-terminal radicals,

the terminal radicals being selected from the group consisting of hydrogen; alkyl; aryl; alkenyl; allyl; trialkylsilyl; alkyl diarylsilyl; dialkylarylsilyl; tri (alkoxy) silyl; fluorine; chlorine; bromine; cyanide; alkoxy; orthoformyl; trialkylsiloxy; acyloxy that include an aryloxy, alkoxy, aryl, alkyl or alkenyl radical; aryloxy; trifluoromethyl; sulphonyl; and acyl that include an alkyl, alkenyl, or aryl radical; and

the non-terminal radicals are selected from the group consisting of alkyl; cyclic alkyl; fully or partially saturated ring alkyl fused to the benzene ring of the anilide at R'a and R'b or at R'b and R'C; partially saturated alkene; partially saturated alkene ring; aryl; heteroaromatic that excludes sulfur; heterocyclic that excludes sulfur except as sulphone; heterocyclic that are partially or fully saturated fused to the benzene ring of the anilide at R'a and R'b or R'b and R1C that exclude sulfur except as the sulphone moiety; ketone; ester; ketal; acetal; ether; dialkylarylamine; nitrile; amide except amide having a nitrogen bonded to hydrogen and an aryl group; urea except urea having a nitrogen bonded to hydrogen and an aryl group; thioamide except thioamide having a nitrogen bonded to hydrogen and an aryl group; thiourea except thiourea having a nitrogen bonded to hydrogen and an aryl group; urethane except urethane having a nitrogen bonded to hydrogen and an aryl group; thiourethane except thiourethane having a nitrogen bonded to hydrogen and an aryl group; a -unsaturated ketone or ester; sulphone; sulphonamide; imide; diarylketone; lactone; lactam; lactim; sultam; sultim; allylsilane; arylsilane; vinylsilane; alkylsilane; silyl ether; siloxane; orthosilicate; silicate; carbonate; orthoester; with the proviso that at least one ortho position of the anilide must be hydrogen and not occupied by R'a, R'b, or R"; and R2, R3, R', R5, and R6 are each independently selected from a group of terminal and non-terminal radicals, the non-terminal radicals potentially including further extensions with one or more terminal or non-terminal radicals,

the terminal radicals being selected from the group consisting of hydrogen; alkyl; aryl; alkenyl; allyl; alkynyl; propargyl; trialkylsilyl; alkyl diarylsilyl; dialkylarylsilyl; tri (alkoxy) silyl; fluorine; chlorine; bromine; cyanide; alkoxy; orthoformyl; trialkylsiloxy; acyloxy that include an aryl, alkyl or alkenyl radical; aryloxy; trifluoromethyl; sulphonyl; and acyl that include an alkyl, alkenyl, or aryl radical; and

the non-terminal radicals being selected from a group consisting of alkyl; cyclic alkyl; bridging saturated or partially saturated alkyl ring; bridging heterocyclic ring not containing sulfur except as the sulphone moiety; olefin; cyclic olefin; aryl; alkynyl; heteroaromatic not containing sulfur; heterocyclic group not containing sulfur except as a sulphone; ketone; ester; ketal; acetal; ether; dialkylarylamine; nitrile; amide except amide having a nitrogen bonded to hydrogen and an aryl group; urea except urea having a nitrogen bonded to hydrogen and an aryl group; thioamide except thioamides having a nitrogen bonded to hydrogen and an aryl group; thiourea except thiourea having a nitrogen bonded to hydrogen and an aryl group; urethane except urethane having a nitrogen bonded to hydrogen and an aryl group; thiourethanes having a nitrogen bonded to hydrogen and an aryl group; a -unsaturated ketone or ester; sulphone; sulphonamide; imide; diarylketone; lactone; lactam; lactim; sultam; sultim; allylsilane; arylsilane; vinylsilane; alkylsilane; silyl ether; siloxane; orthosilicate; silicate; carbonate; orthoester; with the proviso that R2, R3, R4, R5s cannot be fluorine, chlorine, bromine, cyanide, amino, alkylamino, dialkylamino, arylamino, diarylamino, arylamido, arylthioamido, arylcarbonyl, arylthiocarbonyl, alkoxy, trialkylsilyloxy, or acyloxy radicals that incorporate alkyl, alkenyl, or aryl radicals; with the further proviso that R2, R3, R4, R5s cannot include any radical that has a double or triple bond or an aryl or heteroaromatic groups that is conjugated with the y, 8 unsaturation of the anilide-linked-alkene; with the further proviso that R5s cannot be a sulphonyl radical, a vinylic radical unless a complex mixture of products is desired or R5 is the same as CR4CR2R3 radical.

6. The process, according to claim 1, further comprising the following additional step, performed prior to said polycyclizing step:

coupling a P, γ -unsaturated alcohol or thiol with an aryl amine and phosgene or thiophosgene in a three way reaction for producing the anilide-linked-alkene selected from a group consisting of arylcarbamoyle-alkene and arylthiocarbamoyle-alkene, as represented by the following reaction:

and the anilide-linked-heterocycle from said polycyclizing step is represented by the following structure:

wherein the anilide-linked-alkene resulting from said coupling step and the anilide-linked heterocycle resulting from said polycyclization step are limited by said coupling step as follows:

X1 is selected from the group consisting of oxygen and sulfur; X2 is oxygen; R1a, R1b, and R1c are each independently selected from a group of terminal and non-terminal

radicals, the non-terminal radicals potentially including further extensions with one or more of the terminal or non-terminal radicals,

the terminal radicals being selected from the group consisting of hydrogen; alkyl; aryl; alkenyl; allyl; trialkylsilyl; alkylidiarylsilyl; dialkylarylsilyl;

tri (alkoxy) silyl; fluorine; chlorine; bromine; cyanide; alkoxy; orthoformyl; trialkylsiloxy; acyloxy that include an aryloxy, alkoxy, aryl, alkyl or alkenyl radical; aryloxy; trifluoromethyl; sulphonyl; and acyl that include an alkyl, alkenyl, or aryl radical; and

the non-terminal radicals are selected from the group consisting of alkyl; cyclic alkyl; fully or partially saturated ring alkyl fused to the benzene ring of the anilide at R'a and R'b or at R'b and R'c; partially saturated alkene; partially saturated alkene ring; aryl; heteroaromatic that excludes sulfur; heterocyclic that excludes sulfur except as sulphone; heterocyclic that are partially or fully saturated fused to the benzene ring of the anilide at R'a and R'b or R'b and R'c that exclude sulfur except as the sulphone moiety; ketone; ester; ketal; acetal; ether; dialkylarylamine; nitrile; amide except amide having a nitrogen bonded to hydrogen and an aryl group; urea except urea having a nitrogen bonded to hydrogen and an aryl group; thioamide except thioamide having a nitrogen bonded to hydrogen and an aryl group; thiourea except thiourea having a nitrogen bonded to hydrogen and an aryl group; urethane except urethane having a nitrogen bonded to hydrogen and an aryl group; thiourethane except thiourethane having a nitrogen bonded to hydrogen and an aryl group;

(x, P-unsaturated ketone or ester; sulphone; sulphonamide; imide; diarylketone; lactone; lactam; lactim; sultam; allylsilane; arylsilane; vinylsilane; alkylsilane; silyl ether; siloxane; orthosilicate; silicate; carbonate; orthoester;

with the proviso that at least one ortho position of the anilide must be hydrogen and not occupied by R'a, R'b, or R"; and

R2, R3, R4, and Rs are each independently selected from a group of terminal and non terminal radicals, the non-terminal radicals potentially including further extensions with one or more terminal or non-terminal radicals,

the terminal radicals being selected from the group consisting of hydrogen; alkyl; aryl; alkenyl; allyl; alkynyl; propargyl; trialkylsilyl; alkylidiarylsilyl;

dialkylarylsilyl; tri (alkoxy) silyl; fluorine; chlorine; bromine; cyanide; alkoxy; orthoformyl; trialkylsiloxy; acyloxy that include an aryl, alkyl or alkenyl radical; aryloxy; trifluoromethyl; sulphonyl; and acyl that include an alkyl, alkenyl, or aryl radical; and

the non-terminal radicals being selected from a group consisting of alkyl; cyclic alkyl; bridging saturated or partially saturated alkyl ring; bridging heterocyclic ring not containing sulfur except as the sulphone moiety; olefin; cyclic olefin; aryl; alkynyl; heteroaromatic not containing sulfur; heterocyclic group not containing sulfur except as a sulphone; ketone; ester; ketal; acetal; ether; dialkylarylamine; nitrile; amide except amide having a nitrogen bonded to hydrogen and an aryl group; urea except urea having a nitrogen bonded to hydrogen and an aryl group; thioamide except thioamides having a nitrogen bonded to hydrogen and an aryl group; thiourea except thiourea having a nitrogen bonded to hydrogen and an aryl group; urethane except urethane having a nitrogen bonded to hydrogen and an aryl group; thiourethane except thiourethanes having a nitrogen bonded to hydrogen and an aryl group;

the non-terminal radicals being selected from a group consisting of alkyl; cyclic alkyl; bridging saturated or partially saturated alkyl ring; bridging heterocyclic ring not containing sulfur except as the sulphone moiety; olefin; cyclic olefin; aryl; alkynyl; heteroaromatic not containing sulfur; heterocyclic group not containing sulfur except as a sulphone; ketone; ester; ketal; acetal; ether; dialkylarylamine; nitrile; amide except amide having a nitrogen bonded to hydrogen and an aryl group; urea except urea having a nitrogen bonded to hydrogen and an aryl group; thioamide except thioamides having a nitrogen bonded to hydrogen and an aryl group; thiourea except thiourea having a nitrogen bonded to hydrogen and an aryl group; urethane except urethane having a nitrogen bonded to hydrogen and an aryl group; thiourethane except thiourethanes having a nitrogen bonded to hydrogen and an aryl group; ass-unsaturated ketone or ester; sulphone; sulphonamide; imide; diarylketone; lactone; lactam; lactim; sultam; sultim; allylsilane; arylsilane; vinylsilane; alkylsilane; silyl ether; siloxane; orthosilicate; silicate; carbonate; orthoester; with the proviso that R2, R3, R4, Rus cannot be fluorine; chlorine; bromine; cyanide; amino; alkylamino; dialkylamino; arylamino; diarylamino; arylamido; arylthioamido; arylcarbamoyl; arylthiocarbamoyl; alkoxy; trialkylsilyloxy; and acyloxy incorporating a alkyl, alkenyl, and aryl radical; with the further proviso that R2, R3, R4, Rus cannot be radicals that have double or triple bonds or aryl or heteroaromatic groups that are conjugated with the y, b unsaturation of the anilide-linked-alkene; with the further proviso that RS cannot be a sulphonyl radical, a vinylic radical unless a complex mixture of products is desired or R5 is the same as CR4CR2R3 radical.

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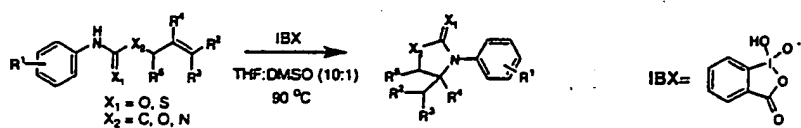


Figure 1

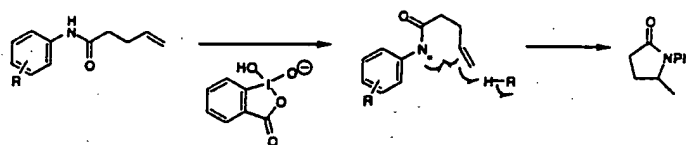


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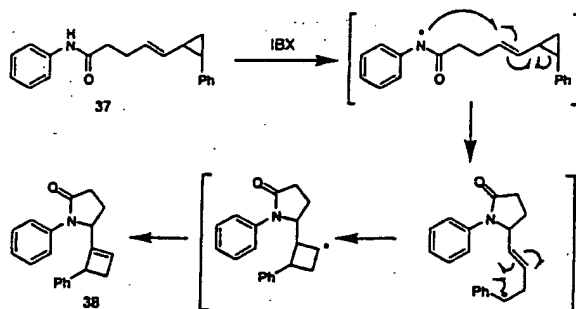


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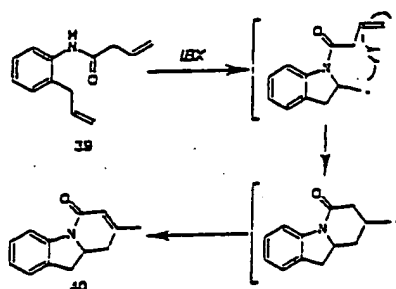


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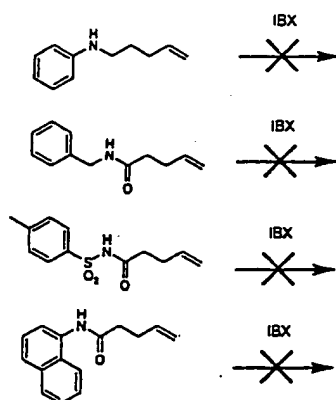


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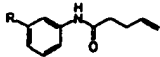
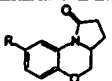
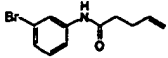
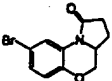
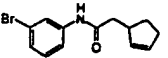
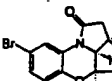
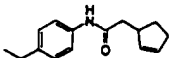
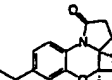
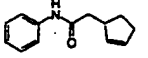

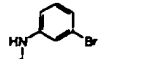

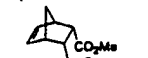

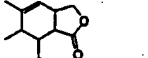

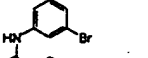

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Figure 6

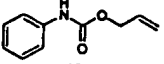

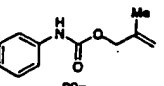

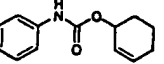
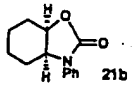

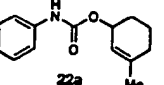
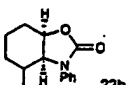

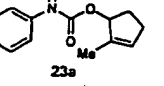
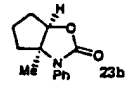
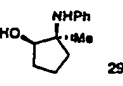
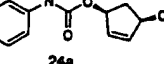
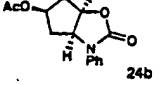
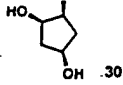
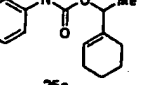
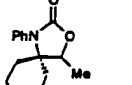
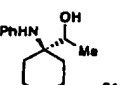
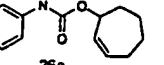
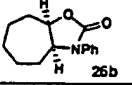
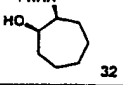
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5	 23a	 23b	88	 29	98
6	 24a	 24b	95	 30	95
7	 25a	 25b	76	 31	90
8	 26a	 26b	83	 32	95

Figure 7

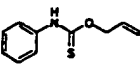

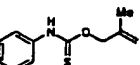

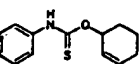
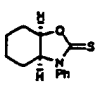
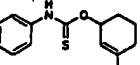
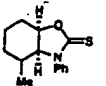
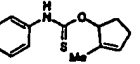
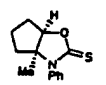
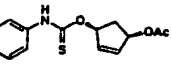
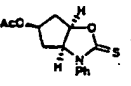
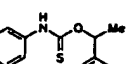
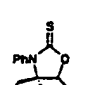
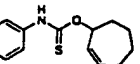
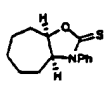
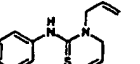
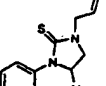
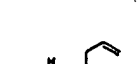


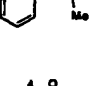
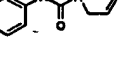
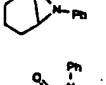
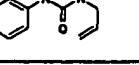
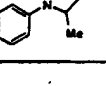
Entry	Starting Material	Product	YIELD
1			-
2			-
3			88
4			-
5			-
6			-
7			-
8			-
9			-
10			-
11			90
12			70
			-

Figure 8

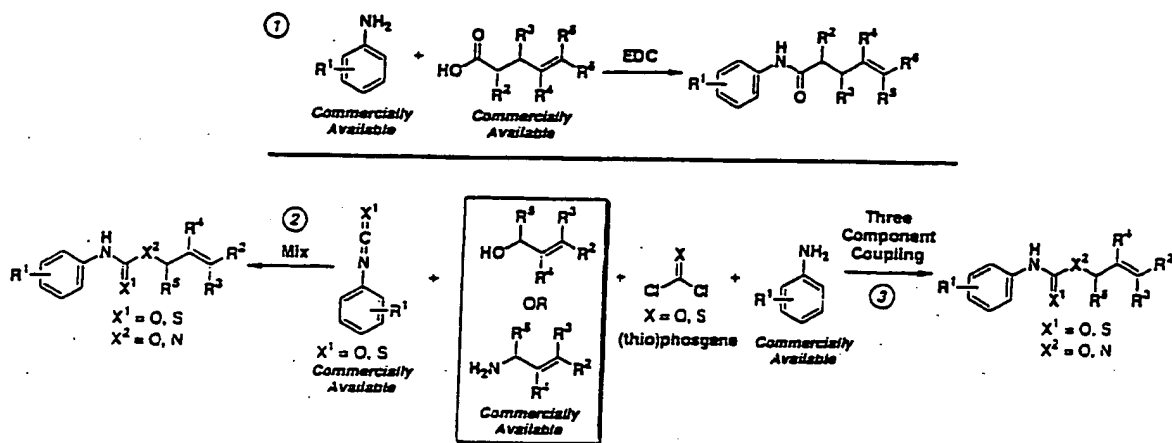


Figure 9

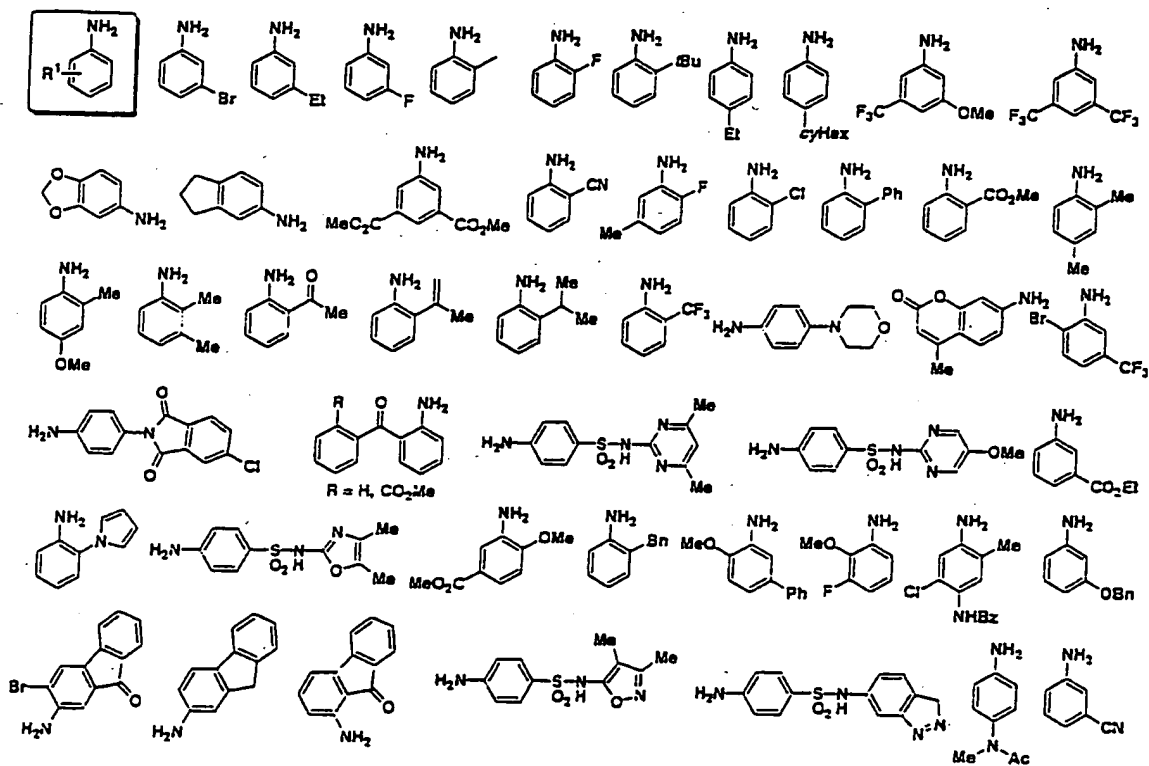


Figure 10

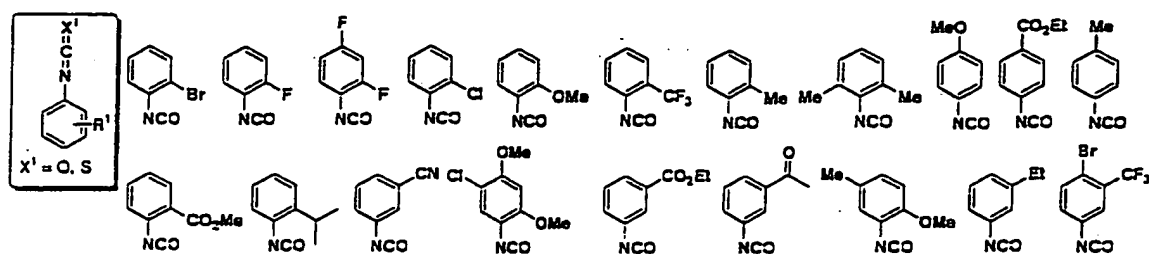


Figure 11

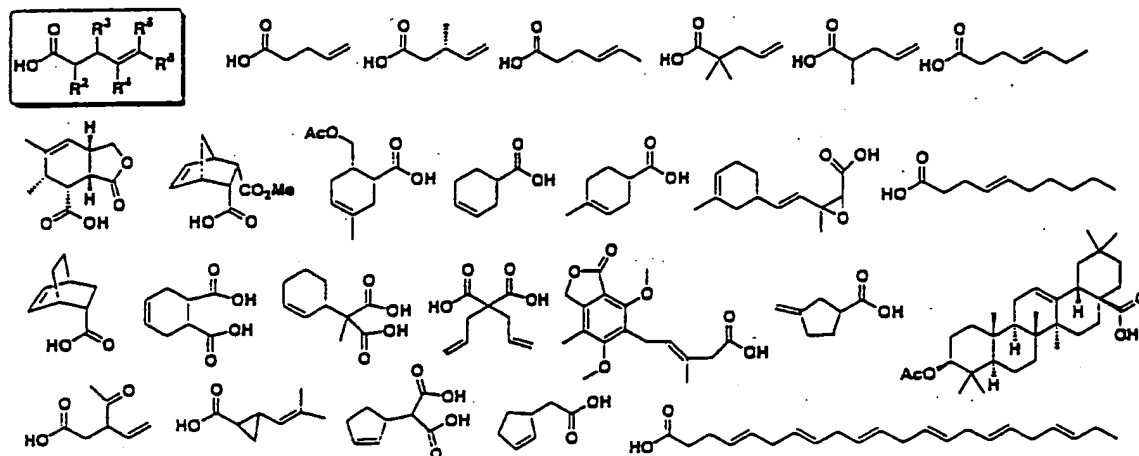


Figure 12

Figure 13

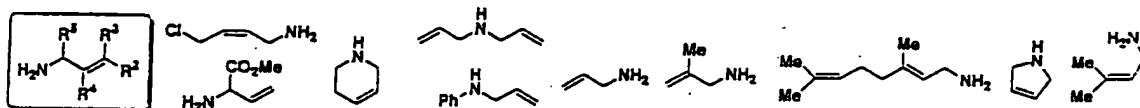


Figure 14

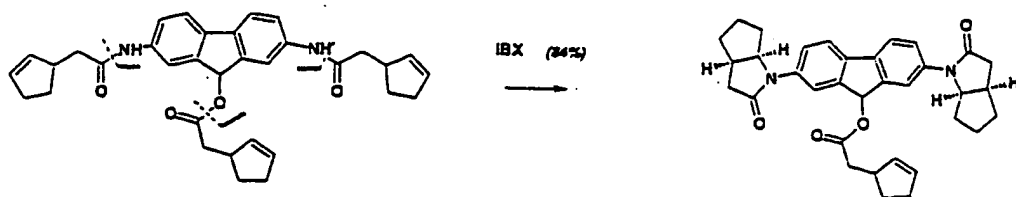


Figure 15

